EXHIBIT A

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The influence of medication on erectile function

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Introduction

Several physiological mechanisms are involved in erectile function. A negative influence of prescription-drugs on these mechanisms will not always come to the attention of the clinician, whereas a drug causing priapism will rarely escape the attention.

When erectile function is influenced in a negative way compensation may occur. For example, age-related penile sensory disorders may be compensated for by extra stimulation.[1] Diminished influx of blood will lead to a slower onset of the erection, but may be accepted. A mild 'venous leak' can be compensated by extra inflow of blood[2] and the suboptimal rigidity may be accepted. Therefore a negative influence of medication on the erectile function will not always lead to a complaint.

The problems themselves for which drugs are prescribed, such as cardiovascular disease, psychosis, depression, diabetes mellitus may have a n gative effect on sexual and erectile function. In this situation the already compromised system is more vulnerable to adverse effects of medication. Erron ously the erectile dysfunction may be attributed to the disease, instead of the medication. In g riatric patients, who often use several medicines at the same time, the issue is even further complicated.[3]

Many patients will not discuss their sexual problems when not invited to do so. In clinical practice all this will result in an underestimation of the drug factor in impotence. It has been estimated that the drug factor plays a role in 25% of patients seeking advice for erectile dysfunction.[4] Patient compliance concerning correct medication usage, is, among other things, dependent on side-effects. In a large follow-up program 8.3% of the male patients stopped their antihypertensive treatment over a five year period, because of side-effects on sexual function.[5] In the drug registration procedures sexual function is not a major issue. This means that knowledge of the problem is mainly dependent on case reports and the lists from side effect registries.[6–8]

Another way of looking at the problem is combining available data on mechanisms of action of drugs with the knowledge of the physiological mechanisms involved in erectile function. The advantage of this approach is that remedies may evolve from it.

In this paper we will discuss the subject in the following order:

Physiology:
- Penile erection
- Control mechanisms
  - hormonal system
  - central nervous system
  - peripheral nervous system
- Cavernous tissue function

Prescription drugs:
- psychotropic drugs
- cardiovascular drugs
- miscellaneous drugs
- drugs to treat erectile disorders

Guidelines for clinical practice

Penile erection

An extensive review on the physiology of penile erection has been published by Andersson.[9] The initiation of an erection is a neurogenic event. The impulses may originate from the brain (as in REM sleep erections) or derive from sacral reflexes (as in some paraplegic patients). In normal circumstances it will be a combination of both. Dilatation of the arteria cavernosa and the helicine arteries is con-

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trolled by the well described neural regulation mechanisms. This is howev r not sufficient for the d velopment of a rigid erection, since there are shortcuts to the venous channels and the resistance of the lacunar spaces in the corpora cavernosa depends on smooth muscle tone. Relaxation of the smooth muscle cells is necessary for the expansion of the corpora, this is initiated by parasympathetic impulses. Sympathetic tone needs to be reduced, since this causes contraction of the smooth muscle cells. The search for non cholinergic, non adrenergic (NANC) transmission of the impulses of the nervous system to the smooth muscle cells has drawn attention to nitric oxide (NO) as an initiator of a cascade of chemical events that results in relaxation of all the smooth muscle cells of the corpora.[10,11] After the first impulses, the scarcely innervated network of endothelial cells and smooth muscle cells take care of their own coordination in order to relax all at the same time. This is accomplished through tight junctions and gap junctions. Free inflow of blood is allowed in the lacunae, finally resulting in such a tumescence that outflow of blood will be stopped by compression of the venous channels between the distended corporal tissue and the tunica albuginea. This leads to rigidity of the penis that may be further enhanced by contractions of pelvic floor muscles, compressing the crurae of the corpora cavernosa and building a pressure that is higher than the systolic blood pressure.[12] Inflow of blood to the corpora cavernosa is minimal at that point. The erection comes to an end by renewed contraction of the smooth muscle cells, initiated by sympathetic impulses and by the production of substances such as endotheline-1, prostaglandin F2α and tromboxane A2 by the endothelial cells.[9,13] This will allow venous outflow by decompression of the subtunical venous plexus.

Control mechanisms

Several control mechanisms play a role in sexual behavior and erectile function. Many have effects on the central nervous system as well as on the cardiovascular system. There is an analogy in the responses of blood vessels to these regulation mechanisms and the responses of the tissue in the corpora cavernosa.

Hormonal system

The exact role of testosterone on erectile function is not well defined. The negative influence of castration on libido is regularly seen in clinical practice. The negative ff ct of castration on erectile function may be secondary to this. Erections during REM sl ep are inhibited by castration, suggesting an influence on the central nervous system.[14,15]

The adult corpus cavernosum hardly has any receptors for testosterone, while in children testosterone induces growth of the penis, rather than erections.[16] It has been shown that the hormonal manipulation preceding gender reassignment (pharmacological castration) lowers the amount of nitric oxide synthase (NOS) in the corpus cavernosum tissue.[17] In a rat model nitric oxide mediated erectile activity was a testosterone dependent event, while in another rat model it was shown that dihydrotestosterone levels positively correlate with the amount of NOS in the corpus cavernosum.[18,19] However, after castration the local mechanisms leading to penile smooth muscle relaxation are not impaired, possibly since compensation occurs by lowering of the sympathetic tone.[20]

The testosterone serum level is mainly determined by the epiphyse/pituitary/testes feedback system. Estrogens and steroid-antiandrogens influence the testosterone serum level via this system. High prolactin levels also lower the testosterone production. Hyperprolactinaemia may be drug induced. Cimetidine, estrogens, metoclopramide, α-methyldopa, morphine and the phenothiazines are known for this. The elevation of prolactin serum levels is usually mild and not accompanied by a decrease in serum testosterone levels. In absence of a low testosterone serum level the relation of hyperprolactinaemia and impotence is unclear and withdrawal of the culprit drug maybe disappointing because of other organic factors determining th erectile dysfunction.[21]

Some drugs have an unexpected anti-androgen effect such as H2-antagonists and some antifungal drugs. Effects on the testosterone levels have been described of beta blockers, spironolactone and digoxin, the practical value of these reports is unclear.[22–24]

Central nervous system

Emotional and cognitive factors influencing sexual behavior and erectile function are beyond the scope of this review. Several parts of the brain are involved in sexual function and already on this central l vel integration with autonomous regulation of other body functions is present. The brain may inhibit or facilitate the spinal mechanisms leading to an erection. Among others, the hypothalamic and limbic pathways are intensively studied. The medial preoptic hypothalamic area, in contact with the paraventricular nucleus of the hypothalamus is important for autonomic and neuroendocrine inte-

gration.[9] Dopaminergic systems and serotoninergic systems play a major role in sexual behavior and erectile function.[25] For several psychopharmaca these systems are the specific target.[26] Apomorphine, a central dopamine agonist, is effective in enhancing sexual behavior in the animal model as well as in humans.[27] For this effect testosterone needs to be present.[28] There is evidence that this effect is also dependent on oxytocine release.[9] Dopamine also has cardiovascular effects, mediated by several distinct types of receptors that vary in their affinity. In low concentrations dopamine acts on vascular D1 receptors, leading to vasodilatation. In somewhat higher doses it activates the beta-1 adrenoceptors, whereas at high concentrations vasoconstriction is effectuated via activation of vascular alpha-1 adrenoceptors.[20]

Of the serotoninergic system mainly the 5-HT_{1A}, 5-HT_{1C} and the 5-HT_2 receptor subtypes play a facilitory role in human sexual behavior and antagonists have a negative influence.[25,26] On this level the explanation may be found why such a marked difference was shown between the effectiveness of several anti-serotoninergic agents in impotence treatment.[30]

For a stimulatory effect of 5-HT_{1A} agonists testosterone needs to be present.[31] Cardiovascular effects of serotonine may be constricting or dilating, depending on the type of receptor activated, while serotonine also influences the release of noradrenaline from adrenergic nerves and stimulates endothelial cells to release prostaglandins and NO.[29]

Noradrenergic neurons also play a role in the central regulation of sexual function.[9] Methyldopa, an older antihypertensive drug, may so be responsible for erectile dysfunction.[6] The selective alpha-2 adrenoceptor antagonist yohimbine may improve libido and its main effect in vivo is probably on the central nervous system.[32] Of the central neurotransmitters oxytocin, ACTH and related peptides, prolactin, gamma-aminobutyric acid and endorphins are all implicated in the regulation of sexual behaviour and erectile function.[9] Stress may influence the production of endogenous opioids which has reflections on the hypothalamic-pituitary-luteinizing hormone axis.[33]

Peripheral nervous system

Somatic pathways are important for sensitivity of the penile skin and the contraction of the pelvic floor muscles. The autonomic nervous system is essential for erectile function. The pharmacology of the autonomic system has been extensively studied. At the ganglionic level (the nicotinic acetylcholine receptor) the system will respond to drugs in the usual way. At this site integration of parasympathetic and sympathetic impulses takes place and the mechanisms of homotropic and heterotropic interaction can be influenced by drugs. The pelvic ganglions are also the site where neuromodulation takes place by various endogenous substances (serotonin, adenosine, histamine, enkephalin and dopamine) at their specific receptors.[29] At the peripheral level the existence of different receptor subtypes and the relative affinity of drugs to these receptors makes prediction of the resulting effect of drugs on the corporal smooth muscle tissue complicated.

Sympathetic nervous system

The smooth muscle has a resting tone that is mainly governed by tonic alpha receptor stimulation.[34] Reduction of sympathetic tone is important to initiate a reaction, but does not result in penile erection. Bilateral sympathectomy does not cause priapism. Psychogenic inhibition of erections is mediated by the sympatic nerves and by circulating catcholamines.[35] Ejaculation is controlled by the sympathetic nervous system. Thereafter detumescence is initiated by the sympathetic pathway, inducing contraction of the smooth muscles of the corpora cavernosa and so allowing outflow of blood. Reviewing the subject of receptors, Andersson concludes that for the cavernosal tissue alpha-1 adrenoceptors predominate functionally, alpha-1A and alpha-1C being more numerous than alpha-1B adrenoceptors.[9] Alpha-2 adrenoceptors predominate in the cavernous artery.[9] The beta-2 adrenoceptors, although present, are not supposed to be functionally important.[36] For impotence treatment with drugs applied intracavernously (i.c.) the alpha adrenoceptors are an important target.[37] Blockade of alpha adrenoceptors by medication may cause priapism.[38]

Parasympathetic nervous system

Transection of the nervi erigenti leads to impotence because the induction of smooth muscle relaxation, followed by high inflow of blood, is a parasympathic event.[39] The parasympathetic impulse however is not only the result of direct cholinergic transmission by acetylcholine to muscarine receptors on the smooth muscle cells in the corpora cavernosa. It is supposed to have its effect by inhibiting the release of noradrenaline from sympathetic nerve endings and by the release of Non Cholinergic Non Adrenergic (NANC) transmitters from the parasympathetic nerve endings and from the endothelial cells.[9,40] NO is one of the main NANC transmitters.[10,11]

Cavernous tissue functi n

From his experience with i.c. injection therapy Goldst in[41] formulat d a cascade theory, in which he combines pharmacologic events with physiology and anatomy. After an i.c. injection with vaso-active drugs relaxation on that site in the cavernous tissue leads to local increase of blood inflow. This if followed by activation of endothelium-mediated relaxation factors, the zone of muscle relaxation is enlarged, leading to local increase of blood inflow etc. If any part of the corpora cavernosa is not completely relaxed, venous return is not sufficiently stopped and rigidity is suboptimal or of short duration. This is the equivalent of the clinical concept of 'venous leakage' that may be quantified by cavernosometry.[42] The pathways by which the smooth muscle cells communicate and the role of the endothelial cells of the corpora cavernosa are under investigation.

The smooth muscle cells are in contact with each other through gap junctions. In cavernous tissue they consist mainly of calcium and potassium channels.[43,44,51] In this way integrated action is possible, since this allows for relatively unimpeded intercellular transit of current carrying ions and transit of small metabolites and second messengers as inositol triphosphate, cyclic adenosine monophosphate (cAMP) and cyclic guanosine monophosphatase (cGMP). For more details we refer to excellent reviews on this matter from Andersson and Christ.[9,45]

Several products of the nerve endings and the endothelial cells can initiate smooth muscle relaxation, such as NO, vasoactive intestinal peptide (VIP), neuropeptide Y, calcitonin gene related peptide, substance P, prostanoids.[46,47] Especially NO has drawn much attention as an important regulator of smooth muscle tone in the corpora cavernosa.[10,11] NO is produced by autonomic nerve endings and by endothelial cells from L-arginine and molecular O_2 by NO synthase (NOS). NOS is available in several isoforms and its production can be stimulated in s veral ways.[48] In chronic hypoxic states NO formation is reduced.[49]

NO activates guanylate cyclase, the conversion of GTP to cGMP lowers the calcium concentration and leads to relaxation of the smooth muscle. In addition to the cGMP pathway, activation of NA/Ka-ATPase may also play a role in the relaxation of corpus cavernosum tissue by NO.[50] Cyclic nucleotide phosphodiesterases (PDE) are enzymes that hydrolyse cGMP and cAMP to monophosphates. PDE may be blocked by pharmaca, for example papaverine.[51,52] Several PDE subtypes can be identified. In the corpora cavernosa PDE_5 is predominant and this subtype is blocked by sildenafil.[53,54] These insights in the physiology of the corpus cavernosum have already led to new possibilities for i.c. injection therapy, for example the use of the NO donors linsidomin and of calcitonin gene related peptide.[55,56] The data from r search of oral medication acting on these systems becomes available now.[53,54,57]

Prescription drugs

Psychotropic drugs

Especially antipsychotic and antidepressant drugs are known for their side effects on erectile function.[6–8] In clinical practice the patients in need of these drugs may not be ideal candidates to have their sexual performance evaluated. Much is known from animal studies. Side effects may be due to adrenergic, anticholinergic, dopaminergic or serotoninergic effects.[58] Other psychotropic drugs such as benzodiazepines, are reported to cause impotence. Maybe this effect is simply the result of sedation.[6] Unexplained is the finding that lithium when combined with benzodiazepines is associated with sexual dysfunction in almost half of the patients.[59]

Antipsychotics and antidepressants have an effect on the dopaminergic and the serotinergic central nervous system that may be stimulating or inhibiting. The combination of stimulating central effects with periferal alpha-blocking properties may induce priapism, because the alpha receptors in th cavernous tissue are important for contraction of smooth muscle cells and so the initiation of detumescence. The most reported antidepressant drug that causes priapism is trazodone.[60] This antidepressant drug has been applied i.c. and induced smooth muscle relaxation.[61] It is also known for its ability to improve libido.[62,63] Clomipramine, a tricyclic antidepressant that combin s serotonin reuptake inhibitor properties with alpha blocking properties is more effective for treatment of premature ejaculation, than for treatment of erectile dysfunction.[64] Fluoxetine has been associated with erectile dysfunction as well as with the return of potency.[8,65] More consistent is its postponing effect on the ejaculation.[66] When erectile dysfunction is caused by a tricyclic antidepressant drug it may be rational to try the patient on trazodon or fluoxetine instead.[67] However one must consider the possibility that erectile dysfunction might persist in the presence of an increased libido.

Of several antipsychotics the alpha-blocking properties are known, so in case of drug induced impotence one might consider an alternative drug with stronger alpha-blocking properties, a higher affinity for the alpha-1 receptor. The affinity for the alpha-1 receptor in decreasing order is: thioridazine,

levopromazine, clozapine, zuclopentixol, haloperidol, bromperidol, pimozide.[68] When the alpha-blocking properties induce priapism, an alternative antipsychotic must b used with a lower affinity to the receptor. The susceptibility of the patient may chang with time and also co-medication with alpha-blocking properties must be considered. Recurrent priapism due to depot zuclopentixol has been reported.[69]

Cardiovascular drugs

To initiate an erection a generous inflow of blood is needed. The classical combination of claudicatio intermittents and impotence, due to stenosis of central arteries is known as the Leriche syndrome. Arteriosclerosis is accompanied by degenerative changes in the corpus cavernosum.[70,71] These changes make the veno-occlusive mechanism less ffective. Dysfunction of the corpus cavernosum tissue is the main cause of 'venous leakage'.[42] The combination of inflow reduction with a diminished possibility to trap the blood in the penis, is detrimental for erectile function.[2] The patient in need of cardiovascular drugs already has a vulnerable erectile function and they will be more susceptible for medication induced erectile dysfunction. In addition to this, many cardiovascular drugs have a direct influence on the autonomous innervation of the penis. Betablocking agents are known for their negative effects on erectile function. This may be due to their effect on the beta adrenoceptors in the corpora cavernosa, but these are underrepresented in the cavernous tissue (alpha receptors outnumber beta adrenoceptors 10–1).[36] Anoth r explanation is a change in balance between alpha and beta sympathetic influence, resulting in insufficient antagonism of the alpha-1 vasoconstriction.[72] When betablocking agents prescribed for high bloodpressure cause impotence, an alpha-blocking agent may be a good alternative. Even alphablocking ag nts have been implicated as the cause of erectile dysfunction.[7,8] This may be due to the lowering of th bloodpressure as such.[73] Possibly making these patients more vulnerable for a steal phenomenon. Alphablocking agents have an effect on the ejaculation, they may delay ejaculation or cause a retrograde ejaculation and so give rise to secondary (psychogenic) erectile dysfunction. Alphablockers interfere with the sympathetic induced detumescence and may cause priapism.

Several vasodilators have a relaxing effect on the corporal tissue when applied intracavernously or even topically, but this effect is not obvious when these drugs are taken orally. Many vasodilators act upon the calcium and potassium channels. Calcium reentry blocking agents are considered safe treatment as far as rectile function is concern d.[74] On cavernous smooth muscle they hav a relaxing effect.[75] When injected i.c. th y induce erections.[76] However th y are reported as responsible for erectile dysfunction.[7,8] This may be due to the drop in blood pressure, provoking a sympathetic nervous syst m response.[76] Potassium channel openers, with pinacidil as well studied example, do show an erectogenic effect when directly applied to the corporal tissue. But taken orally potassium channel openers are not suitable for impotence treatment because of insufficient tissue selectivity and the stimulation of the sympathetic nervous system.[77–79] Minoxidil is an exception in this respect, being applied as ointment for induction of tumescence, while taken orally it has been reported to cause priapism.[80]

The above mentioned mechanisms may play a role in impotence caused by ACE-antagonists. Since angiotensin converting enzyme (ACE) inhibitors may be responsible for gynecomastia, a hormonal influence also seems possible.[81] The older cardiovascular drugs have important effects on the central nervous system, for example methyldopa influencing central alpha-2 activity.[6] Erectile disorders caused by diuretics have been reported, the mechanism is unknown. Digoxin-associated impotence has recently been studied extensively and the underlying mechanism was shown to be inhibition of the Na/Ka-ATPase pump.[82] The authors even remarked that digoxin might prove useful to inhibit erectile activity, for example after penile surgery.

In only a few comparative studies of different bloodpressure lowering regimes sexual function has been evaluated. In a trial with 626 men in need of antihypertensive treatment, 44% had a complaint on sexual functioning at the start of the trial. Half of these complaints concerned erectile function. The group on the ACE inhibitor captopril had as many patients improving as deteriorating (18%), while the patients on the beta adrenoceptor blocker propranolol and the patients on methyldopa improved in 9% and worsened in 25%. Of the patients who needed additional diuretics later in the trial, the patients on propranolol and a diuretic had extra problems with erectile function.[83] A comparison between a diuretic (hydrochlorothiazide) and an alpha adrenoceptor blocker (prazosin) showed that nocturnal erections were more rigid after the use of the alpha adrenoceptor blocker.[84] In a comparison of chlothalidone, acebutolol, doxazosin, amlodipine, enapril and placebo for hypertension treatment, pre-existing problems with erectile function improved with all patients on doxazosin (an alpha blocking agent).[85] Often cardiovascular drugs have a negative effect on erectile function, but disease related problems and drug related problems are hard to distinguish in the clinical setting. Any cardiovascular drug may cause erectile dysfunction. ACE inhibitors, calcium channel blockers and alpha blockers should be consid-

ered as alternatives in case of drug induced impotence.[74]

Miscellaneous drugs

Histamine H_2-antagonists (used to lower gastric acid secretion) are related to impotence. H_1, H_2 and H_3 receptors have been found in the corpus cavernosum and stimulation leads to contraction of the smooth muscle cells.[86] H_2 receptors are not considered functionally important in the corpora and H_2-antagonists applied i.c. have no effect on erectile function.[86] Therefore the explanation of erectile dysfunction due to H_2-antagonists is probably their anti-androgenic effect.[87] Since these drugs are in the top-ten of prescription drugs the problem is relevant in spite of the probably low frequency in which it becomes manifest. Cimetidine was the first drug from this class associated with impotence, but there is no reason to assume the other H2-antagonists are free of this problem.[8,88] When it occurs, the medication must be changed to a completely different class of drugs, for example antacids.

Analgesics of the nonsteroid anti-inflammatory type (NSAID) are consistently reported as responsible for erectile dysfunction.[7,8] Several prostanoids are synthesized in the corpus cavernosum and they have various effects on the smooth muscle.[89] This may explain the negative effects of some NSAIDs. In practice the problem is not frequently seen, taking into account that these drugs are taken very often.

Anti-androgens, prescribed for prostate cancer, will commonly lead to impotence. This effect is related to lowering testosterone to castration level which is caused by LHRH-agonists and by steroidal antiandrogens. When the patient cannot accept this side effect, it is possible to treat them with nonsteroidal antiandrogens, or treat them intermittently.[90–92] Whether these approaches are oncologically safe, has still to be established. Finasteride, a drug that blocks the conversion of testosterone into dihydrotestosterone and is used for symptomatic benign prostate hyperplasia, has caused impotence in 3.7% of the cases.[93] Recently some doubt is cast on the notion that dihydrotestosterone is not necessary for erectile function.[19]

Drugs to treat impotence

Extensive reviews, for oral medication and for drugs for i.c. use, were published in this journal.[32,94] The alpha-2 adrenoceptor yohimbine has been used for its libido enhancing and its erection improving properties. The main pharmacological property is alpha-blockade. In a double blind study good responses were noted in 21 and 13.8% for 6 mg yohimbine three times daily and placebo.[95] This type of study is necessary before any claim can be made for this indication. Alpha-2 adrenoceptor blockade as such is insufficient for impotence treatment. Recently a study with more than 300 patients using placebo or delequamine orally was stopped because no benefits could be proven.[96] Alpha$_2$-blockade may be rational only in the younger age group with 'pure' psychogenic impotence.[97]

The combination of central effects on the serotinine system combined with periferal alpha adrenoceptor blocking properties as is seen in trazodone, has been advocated for oral impotence treatment.[98] In a double blind placebo controlled trial we were unable to detect any beneficial effect beyond the placebo effect.[99] Combining drugs may give synergistic effects. The combination of 50 mg trazodon with 15 mg yohimbine has recently been reported useful in a group of patients without physical abnormalities detectable. The responders had suffered impotence for a significant shorter period before treatment was started (6 *vs* 18 months).[100]

Apomorphine, a dopamine agonist, can induc erections in patients who have no organic problems, but it has many side effects.[101] The opiate antagonist naltrexone has been tried on idiopathic impotence patients, with positive effects only on the s lf-reported early-morning erections.[102] Presently trials are conducted with drugs that have their rationale in the new insight in corpus cavernosum physiology. The nitric oxide precursor 1-arginine has b n tested, however the preliminary favorable data need confirmation.[57] A trial with oral medication that inhibits type V cGMP-specific phosphodiesterase, UK-92,480 (sildenafil), showed favourable results in impotence patients with no known organic cause.[53,54]

Guidelines for clinical practice

It would be ideal to obtain information on the sexual function of any patient before medication is prescribed. Once the patient has been asked about it, he knows his doctor is interested and the issue can be discussed in the future. When the patient complains about impotence after exposure to a drug, first of all the exact nature of the complaint must be established. Ejaculation disorders must be differentiated from erectile failure. (Ejaculation disorders are also frequently drug related.) The time relationship between the start of the medication and the start of the complaint must be established. When the drug is known to be related to erectile disorders, see Table 1, an alternative drug may be tried. Suggestions are given in the earlier sections. When the drug is not known to cause impotence, detailed follow-up after

Table 1 (*continued*)

primidone	pseudoephedrine	terazosin	tridihexethyl
probucol	ramipril	testosterone	trifluoperazine
prochlorperazine	ranitidine	thiabendazole	trifluperidol
procyclidine	rauwolfia	thiazinamium	triflupromazine
progesterone	reserpine	thiethylperazine	trihexyphenidyl
proguanil	scopolamine	thioridazine	trimeprazine
proloniumiodide	secobarbital	thiothixene	trimetaphan
promazine	selegiline	thiotixene	trimipramine
promethazine	simvastatin	tilidine	triptorelin
propafenone	sotalol	timolol	trospium chloride
propanolol	spironolactone	tranylcypromine	verapamil
propantheline	stilbestrol	trazodone	vincristine
prothipendyl	sulpiride	triamcinolone	vinylbital
protionamide	tamoxifen	triazolam	zopiclone
protriptyline	temazepam	trichlormethiazide	zuclopenthixol

dechallenge is recommended. When erectile function is restored in a reasonable period of time, then a rechallenge should be considered and the case may be reported. Priapism is easy to diagnose. The problem must be treated within 8 h.[103] Delay may impair future erectile function of the patient and may have legal sequelae. In these cases the alpha adrenoceptor blocking properties of future medication must be considered, especially with psychotropic pharmaca, cardiovascular drugs and medication for urinary outflow obstruction.

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